TEST PLAN FOR THIODIPROPIONITRILE (CAS NO. 111-97-7)

OVERVIEW

The Thioesters Association agrees to sponsor thiodipropionitrile (CAS No. 111-97-7) in the U.S. EPA High Production Volume Chemical Program. The sponsors hereby submit a test plan for this substance. It is the intent of the sponsors to use existing data plus additional testing as proposed in the test plan to fulfill the Screening Information Set (SIDS) endpoints.

Table 1. Test Plan Matrix for Thiodipropionitrile (CAS No. 111-97-7)

CAS No. 111-97-7	Information	Estimation	Acceptable	New Testing Required
ENDPOINT	Y/N	Y/N	Y/N	Y/N
PHYS/CHEM PROPERTIES				
Melting Point	Y	N	Y	N
Boiling Point	Y	N	Y	N
Vapor Pressure	Y	N	Y	N
Partition Coefficient	Y	Y	Y	N
Water Solubility	Y	N	Y	N
ENVIRONMENTAL FATE				
Photodegradation	Y	Y	Y	N
Stability in Water	Y	N	Y	N
Biodegradation	N	N	N	Y
Transport between Environmental Compartments (Fugacity)	Y	Y	Y	N
ECOTOXICITY				
Acute Toxicity to Fish	Y	Y	N	NR
Acute Toxicity to Aquatic Invertebrates	Y	Y	N	NR
Toxicity to Aquatic Plants	Y	Y	N	NR
TOXICOLOGICAL DATA				
Acute Toxicity	Y	N	Y	N
Repeated Dose Toxicity	Y	N	N	NR
Genetic Toxicity-Mutation	N	N	N	Y
Genetic Toxicity-Chromosomal Aberrations	N	N	N	Y
Toxicity to Reproduction	N	N	N	NR
Developmental Toxicity	N	N	N	NR
OTHER TOXICITY DATA				
Skin Irritation (NR)	Y	N	Y	N
Eye Irritation (NR)	Y	N	Y	N
Sensitization (NR)	Y	N	Y	N

Y = yes; N = no; NR = toxicity testing is not required because the material is a closed system intermediate (see Appendix I).

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1. Introduction

The Thioesters Association has agreed to supply screening information under the U.S. EPA High Production Volume Chemical Program for thiodipropionitrile. The Thioesters Association consists of the following manufacturers: Cytec Industries, Inc. and the Dow Chemical Company. This plan identifies existing data of adequate quality for this chemical, and outlines the intended testing to be conducted.

2. Designation of Test Substance

The test substance presented in this test plan is 3,3'-thiodipropionitrile (CAS No. 111-97-7). Its chemical structure is as follows:

$$NCCH_2CH_2SCH_2CH_2CN$$

This substance has the following synonyms:

Di(2-cyanoethyl)sulfide
Propionitrile, 3,3'-thiodi
Sulfide, bis(2-cyanoethyl)
Thiodipropionitrile

3. Criteria for Determining Adequacy of Data

All available studies were reviewed and assessed for adequacy according to the standards of Klimisch et al. (1997). Studies receiving a Klimisch rating of 1 or 2 were considered to be adequate.

4. Discussion of Available Test Information

The thiodipropionitrile test plan matrix (as shown in Table 1) was constructed after a careful evaluation of all existing data (see below). This matrix is arranged by study type (columns) and screening data endpoints (rows), and indicates if data are provided for each end point in the sets of robust summaries.

4.1 Chemical and Physical Properties

The results of chemical/physical property testing are shown in Table 2.

4.1.1 Melting Point

A measured melting point of 25 – 29 °C was obtained in a recent study conducted according to OECD Test Guideline 102 (Cuthbert and Mullee, 2003). A melting point of 25ºC is reported by the Cytec Industries, Inc. material safety data sheet. The results are consistent with the physical state of the product at room temperature. The product is in the form of a solid or liquid, or is

Table 2. Chemical/physical properties of thiodipropionitrile

Endpoint	Thiodipropionitrile (CAS No. 111-97-7)
Molecular weight grams/mol	140.20
Melting point	25 – 29 °C[a]
Boiling point	163-4 °C at 1 hPa[a]
Relative density	1.11[a]
Vapor pressure	7.3 x 10E-5 hPa[a] at 25° C
Partition coefficient (Log Pow or Kow)	-0.05 [b]
Water solubility (mg/l at 30 ° C)	25,000 [a]

[a]measured; [b] estimated by EPIWIN

partially solid at ambient temperatures (20-30°C), depending on whether the purity is 96.5% or closer to 99%.

4.1.2 Boiling Point

A measured boiling point of 163-4 °C at 1 hPa has been reported in the Dow Chemical Company material safety data sheet for thiodipropionitrile.

4.1.3 Vapor Pressure

A vapor pressure of 7.3 x 10^{-5} hPa at 25° C has been measured using OECD Test Guideline 104 (Tremain, 2003). The EPIWIN-calculated value is 0.03 hPa at 25° C. Measured inputs to the model were a melting point of 27 ° C, boiling point of 250 ° C at 1013 hPa, vapor pressure of 5.5 E-5 mm Hg, and a water solubility of 25,000 mg/l.

4.1.4 Octanol/Water Partition Coefficient

The EPIWIN Kowwin program provides a calculated partition coefficient of log Kow = –0.05. Measured inputs to the model were a melting point of 27° C, boiling point of 250 ° C at 1013 hPa, vapor pressure of 5.5 E-5 mm Hg, and a water solubility of 25,000 mg/l.

4.1.5 Water Solubility

A measured water solubility value of 25,000 mg/l at 30°C has been reported in the Cytec Industries, Inc. material safety data sheet for thiodipropionitrile. The EPIWIN Wskow program calculates a water solubility of 117,900 mg/l at 25°C.

4.1.6 Summary/Test Plan for Physical Properties

Measured values are available for melting point, boiling point, vapor pressure and water solubility. These values are considered to be sufficient to characterize these endpoints. A

calculated value is available for the partition coefficient, using EPIWIN Kowwin. This value is deemed to be adequate to characterize this endpoint.

4.2 Environmental Fate/Pathways

Results of environmental fate modeling and studies are summarized in Table 3.

Table 3. Environmental fate parameters for thiodipropionitrile

Endpoint	Value
Indirect Photolysis (OH sensitizer) (Hydroxyl Radical Rate Constant)[b] (Atmospheric $T_{1/2}$) [b]	 3.885 E-12 cm3/(molecule*sec) 33 hours
Stability in Water[a]	$T_{1/2}$ > 1 year at 25 º C
Henry's Law Constant[b]	2.38 E-10 atm-m^3/mol
Koc[b]	177.1
Environmental transport (Fugacity Level III mass percentages)[b]	Air = 0.007 Water = 49.3 Soil = 50.6 Sediment = 0.0917
Biodegradation	No measured data, EPIWIN predicts ultimate biodegradation of weeks-months based on the molecular structure

[a]measured; [b] Estimated using EPIWIN

4.2.1 Photodegradation

Photodegradation with hydroxyl radical sensitizer was estimated using EPIWIN/Aop (v1.90). An overall OH rate constant of 3.885 E-12 cm^3/(molecule*sec) was calculated based on the summation of individual rate constants for each bond fragment in the molecule using the program algorithm. A half-life of 33 hours was calculated assuming a constant concentration of OH radical and pseudo first order kinetics.

4.2.2 Stability in Water

According to a recent study conducted according to OECD Test Guideline 111 (Cuthbert and Mullee, 2003), less than 10% of the material hydrolyzes over 5 days in solutions maintained at pH values of 4, 7 and 9 and a temperature of 50 +/- 5 degrees C, and at a physiologically relevant pH and temperature (1.4 and 37 degrees C, respectively). The half-life calculated from the data at pH 4, 7 and 9 was > 1 year at 25 degrees C. However, according to manufacturing information (see Appendix I), hydrolysis of thiodipropionitrile to the corresponding acid salt has been observed at temperatures higher than those used for manufacture (28 - 30ºC).

4.2.3 Fugacity

Level III fugacity modeling has been conducted on the test material using the EPIWIN model. Measured inputs to the program are the melting point, boiling point, and water solubility listed in

Table 2. Emission rates inputted into the program were air: 0 kg/hr, water: 1000 kg/hr, soil: 1000 kg/hr and sediment: 0 kg/hour. The following half-lives were calculated: T ½air = 66 hr, water = 900 hr, soil = 900 hr, and sediment = 3600 hr. The Biowin ultimate value range was weeks to months. A Henry's Law Constant of 2.38 E -10 atm-m^3/mol and a soil sediment partition constant (Koc) of 177.1 were estimated using the EPIWIN/Henry and Pckoc Programs, respectively. The percent mass balances predicted for thiodipropionitrile in air, water, soil and sediment are shown in Table 3. The results indicate that the material will partition to water and soil.

4.2.4 Biodegradation

A study that provides data on the rate and extent of biodegradation of thoidipropionitrile in the aqueous environment is not available. Biodegradation testing is therefore proposed by the sponsors.

4.2.5 Summary/Test Plan for Environmental Fate Parameters

Estimated values are available for the hydroxyl radical induced photolysis rate constant and atmospheric half-life, Henry's Law Constant, soil sediment partition coefficient, and Fugacity Level III environmental transport parameters. No further testing is planned for these endpoints. Biodegradation testing has not been conducted. Since results of the hydrolysis study indicate that the material is fairly stable in water, biodegradation testing is relevant, and will be conducted.

4.3 Ecotoxicity

4.3.1 Acute Toxicity to Fish

The 96-hr LC50 value for fish estimated by the EPA's ECOSAR neutral organics model is 8785.377 mg/l. No measured data are available.

4.3.2 Acute Toxicity to Aquatic Invertebrates

The EPA's ECOSAR neutral organics model predicts a 48-hour EC50 value of 8170.722 mg/l for Daphnia. No measured data are available.

4.3.3 Acute Toxicity to Aquatic Plants

The 96 hr EC50 value calculated for green algae by the ECOSAR neutral organics model is 4539.524 mg/l. No measured data are available.

4.3.4 Summary/Test Plan for Ecotoxicity

LC50 and EC50 toxicity values have been estimated by EPIWIN ECOSAR for fish, Daphnia and green algae. The values for all three species are > 4539 mg/l, which suggests that the material is of low toxicity to these species. Since the material is a site limited, wholly consumed Type A intermediate (see Appendix I), waste streams contain only minimal concentrations of thiodipropionitrile. Therefore, environmental concentrations will be considerably less than those

estimated by ECOSAR to be toxic to aquatic species. For this reason, no aquatic toxicity testing is planned.

4.4 Human Health Data

4.4.1 Acute Mammalian Toxicity

This endpoint is filled by sufficient oral, inhalation and dermal toxicity studies in rodents. The LD_{50} value for the oral study in mice conducted with thiodipropionitrile of > 90% purity is 3.75 g/kg (Tusing, 1953a). Inhalation exposure to a saturated vapor of thiodipropionitrile (containing approximately> 15.5 ppm) for 6 hours did not cause death or signs of toxicity in rats, mice or guinea pigs (Tusing, 1953b). The dermal LD_{50} value in guinea pigs was > 8 ml/kg (8.876 g/kg) (Tusing, 1953a).

Signs of toxicity in mice orally exposed to lethal concentrations included squinting, lacrimation, rapid and labored respiration, ataxia and depression, vasodilation around the mouth, mild clonic convulsions and coma preceding death. Postmortem examinations of mice that died revealed hemorrhagic or hyperemic lungs, distended stomachs, irritated intestines (with vasodilation in some cases), mottled livers and granular kidneys. In addition, blood clots were observed in the region of the transverse sinuses of 2 mice treated with 4.4 g/kg. No other brain damage was observed grossly. Animals that survived until necropsy had normal gross pathology.

4.4.2 Repeated Dose Mammalian Toxicity

Two repeated dose toxicity experiments have been performed with thiodipropionitrile.

Results of a 10-day repeated dose dermal study in rabbits show that application of 1.0 g/kg/day did not cause toxicity in 5/6 animals (Tusing, 1953a). After 6 treatments, one animal developed an apparent weakness or incoordination of the hind extremities. This behavior persisted until study termination. Placement and righting reflexes in this animal were normal. This animal also developed diarrhea, weight loss, and an "unthrifty" appearance. There were no significant necropsy findings in any of the animals (including the animal with diarrhea).

Rats have been given 100, 1,000 and 10,000 ppm thiodipropionitrile in the diet for 32 continuous days (Tusing, 1953b). Based on the average amount of food consumed and average body weights, the amount of test material consumed on a mg/kg/day basis was 10.7, 104.8 and 1010.8 for the 100, 1,000 and 10,000 ppm groups, respectively. In this study, the authors concluded that there was no evidence of toxicity at any dose level. However, one animal exposed to 100 and another to10,000 ppm died during the study. In addition, gross pathological changes in the liver and kidneys were observed in animals treated with 1,000 and 10,000 ppm. Since this study was not conducted according to current standards, it was given a reliability rating of 4 (not assignable).

Although these studies are not up to current standards, no further repeat dose testing is required, since the substance is a Type A industrial intermediate (see Appendix I).

4.4.3 Genetic Toxicity

4.4.3.1 Mutagenicity

Mutagenicity testing has not been conducted. Testing is proposed for this endpoint.

4.4.3.2 Chromosomal aberration

No tests for this endpoint were located. Testing is proposed for this endpoint.

4.4.4 Reproductive and Developmental Toxicity

Reproductive or developmental toxicity tests with thiodipropionitrile have not been performed. Thiodipropionitrile is used exclusively as a closed-system (Type A) industrial intermediate, chemically converted to other products. The potential for significant human exposure is strictly limited. Therefore it is believed that this material qualifies for exemption from reproductive toxicity testing under the established guidelines of the U.S. EPA HPV chemical program. Detailed documentation of the information required to substantiate manufacture and use as a closed-system industrial intermediate with limited exposure is provided in Appendix I of this test plan.

According to the U.S. EPA HPV Chemical program for Type A intermediates, developmental toxicity testing is required. However, due to the precautions involved in use and manufacture of the material (see Appendix I), the possibility for exposure is extremely low. Therefore, we believe that developmental toxicity testing is not necessary.

4.4.5 Additional Data

4.4.5.1 Skin and Eye Irritation

The results of a repeated dose dermal toxicity study in rabbits with material of fairly high purity (> 90%) indicate that 1.0 ml/kg thiodipropionitrile is not irritating to skin (Tusing, 1953b). In an acute study, application of 4.0 ml/kg (but not 8.0 ml/kg) to rabbits caused behavior indicative of burning or pain (Tusing, 1953a). Application of undiluted material to rabbit eyes caused pain, vascularization of the sclera and nictitating membrane and some edema of the upper eyelid that resolved within an hour.

4.4.5.2 Sensitization

The ability of thiodipropionitrile to produce sensitization was tested in modified repeated dose dermal toxicity study in rabbits (Tusing, 1953b). Test material (1.0 ml/kg) was applied dermally 5 days/week for a total of 10 applications, and a challenge dose of 1.0 m/kg was applied after a 10 day rest period. None of the rabbits tested exhibited any evidence of sensitization over the next 5 days.

4.4.6 Summary/Test Plan for Mammalian Toxicity

Adequate acute toxicity studies have been conducted for thidiopropionitrile. Results of these studies show that exposure to fairly large amounts of thiodipropionitrile is required to produce acute toxicity. The material may cause irritation to the skin and eyes immediately after exposure, which quickly resolves.

Results of repeated dose oral and dermal toxicity studies show that fairly high doses of thiodipropionitrile are required to produce toxicity. However, microscopic analyses and laboratory tests that are currently required of repeated dose toxicity studies were not performed. Although these studies are not up to current standards, no further repeat dose testing is proposed, since the substance is a Type A industrial intermediate. No reproductive or developmental toxicity data are available, but no testing is planned for these endpoints, since the substance is a Type A industrial intermediate with extremely low probability of exposure (see Appendix I). No data are available for mutagenicity or, chromosomal aberrations, so this testing is planned.

5. Summary

Physical properties

Adequate data exist to characterize melting point, boiling point, water solubility and partition coefficient. A value for the partition coefficient (log Kow) has been estimated using the EPIWIN KOWWIN program. No physical property testing is proposed.

Environmental fate properties

EPIWIN modeling provides adequate data for hydroxyl radical induced atmospheric photodegradation and environmental transport, as well as bioconcentration factor and Henry's Law Constant. Thiodipropionitrile is known to have limited stability in water and hydrolyses to the corresponding thiodipropionic acid (CAS No. 111-17-1) or its salt, depending on pH and temperature. Measured data indicate that hydrolysis occurs slowly at ambient temperatures. As mentioned earlier, no biodegradation data are available and a biodegradation study is proposed.

Aquatic toxicity

Testing in fish, Daphnia or algae has not been performed. LC/EC_{50} values for thiodipropionitrile in these species have been estimated using ECOSAR. Acute aquatic testing is not proposed for fish, daphnia and algae, since the LC/EC_{50} values predicted by ECOSAR are substantially higher than expected environmental concentrations (See Appendix I for further documentation).

Mammalian toxicity

Adequate acute mammalian toxicity data are available, and no testing is proposed for this endpoint. No data are available for mutagenicity or chromosomal aberrations; therefore testing to fill these endpoints is proposed. No reproductive or developmental toxicity studies are available, but no testing is proposed, because thiodipropionitrile is manufactured and used exclusively as a site limited, closed system (Type A) industrial intermediate and extra precautions are taken to limit exposure (See Appendix I for further documentation). Repeat dose studies are available and summarized. Although these studies are not up to current standards, no further repeat dose testing is required, since the substance is a Type A industrial intermediate.

6. References

American Cyanamid Company. 1953. Data sheet for toxicity study.

Cuthbert JE and Mullee DM. 2003. 3,3'-thiodipropionitrile (CT-781-03): Determination of melting point/melting range and hydrolysis as a function of pH. SafePharm Laboratories (SPL) project number 971/210, dated September 24, 2003 (unpublished).

Cytec Industries Inc. 1997. Material safety data sheet for thiodipropionitrile, dated July 1.

EPIWIN AOP (v1.90).

EPIWIN BCF (v2.14)

EPIWIN ECOSAR (v0.99g)

EPIWIN HENRY (v3.10)

EPIWIN HYDROWIN (v1.67).

EPIWIN KOWWIN (v1.66).

EPIWIN Level III Fugacity modeling program.

EPIWIN MPBPWIN (v1.40).

EPIWIN PCKOC Program (v1.66).

EPIWIN WSKOW (v1.40).

Fieser, L and Fieser, M, Advanced Organic Chemistry, pp 365-6 (1961).

Klimisch HJ, Andreae M and Tillmann U. 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Reg Tox Pharm 25:1-5.

The Dow Chemical Company. 2001. Material safety data sheet for thiodipropionitrile, dated December 3.

Tremain SP. 2003. 3,3'-thiodipropionitrile (CT-781-03): Determination of vapour pressure. SafePharm Laboratories (SPL) project number 971/211, dated September 24, 2003 (unpublished).

Tusing TW. 1953a. Progress Report : B,B' Thiodipropionitrile Acute Oral and Dermal Toxicity and Acute Eye Irritation. Hazleton Laboratories Report to American Cyanamid Company, dated Feb. 24, 1953 (unpublished).

Tusing TW. 1953b. Progress Report : B,B' Thiodipropionitrile Repeated Dermal Application, Acute Inhalation Toxicity, and Subacute Feeding. Hazleton Laboratories Report to American Cyanamid Company, dated March 30, 1953 (unpublished).

APPENDIX I

Documentation of manufacture and use of thiodipropionitrile as an industrial intermediate

According to the EPA Guidance for Testing Closed System Intermediates for the HPV Challenge Program, "any chemical which is intended to undergo a further deliberate reaction to produce another industrial substance is considered an intermediate."

It is believed that thiodipropionitrile is a closed system intermediate that fits the description of a Type A closed system industrial intermediate. This description is as follows:

(a) isolated intermediates which are stored in controlled on-site facilities

The EPA guidance also states that documentation is to be provided to support the claim for reduced testing. Such documentation includes information on number of sites, basis for closed process, and information on release, transportation or presence in distributed product. This information for thiodipropionitrile is provided below:

Thiodipropionitrile is manufactured at two plant sites in the United States. These sites are owned and operated by Cytec Industries Inc. and The Dow Chemical Company (one site per company). At each site, manufacture is carried out in a closed system by the reaction of acrylonitrile with sodium sulfhydrate (SSH) in an aqueous medium. The total number of workers involved in the manufacture and use processes at the two plant sites is approximately 40 for Dow and 8 for Cytec Industries Inc. The reactants are each added to the reactor from closed feed tanks through closed lines. A slight molar excess of SSH is employed to assure complete chemical conversion of acrylonitrile. The reaction temperature is maintained between 28-30°C, since thiodipropionitrile undergoes significant hydrolysis to thiodipropionic acid and its sodium salt at higher temperatures.

The product liquid thiodipropionitrile layer is purified by water washing and separation within the closed reactor, and transported through closed lines to a storage tank. From the storage tank, thiodipropionitrile is transferred on site through closed lines to another reactor for conversion to a different chemical used to manufacture thio chemicals. In addition to the liquid product layer, the reaction process has three other process layers, which are the aqueous alkaline layer containing excess SSH, and two water washes. The water washes are recycled to the process and any waste aqueous layers are sent to plant waste process water treatment facilities for biodegradation. These streams contain minimal concentrations of thiodipropionitrile. The major organic component of these streams is byproduct waste, thiodipropionic acid, sodium salt, which is formed by hydrolysis of the product.

At both Cytec Industries Inc. and the Dow Chemical Company the sole use of thiodipropionitrile is as a closed system industrial intermediate, which is completely converted to other thio chemicals at the same plant site. There are no sales of thiodipropionitrile, the intermediate does

not leave the manufacturing site at either company, and thiodipropionitrile is not present appreciably in any downstream product.

Although no industrial hygiene monitoring data are available for thiodipropionitrile at either manufacturing facility, the closed system manufacturing and conversion processes, coupled with the limited volatility and high boiling point (163-4°C at 1 hPa) of thiodipropionitrile both suggest that any worker exposure to this substance would be infrequent and at a very low level. Extra precautions must be taken (closed system, engineering controls, personal protective clothing as appropriate, etc.) to comply with special, strict Occupational Safety and Health Administration (OSHA) regulations (29 CFR 1910.1045) designed to prevent exposure to acrylonitrile, the raw material used to manufacture TDPN. These regulations have been in place since 1980. The current OSHA TLV for acrylonitrile is 2 ppm. As required by the OSHA regulations, whenever the concentration of acrylonitrile is unknown, a supplied air and auxiliary self-contained breathing apparatus with full facepiece in positive pressure mode is required to minimize exposure to acrylonitrile vapor. In addition, impermeable protective clothing is used to protect any area of the body which may come in contact with liquid acrylonitrile. During maintenance in these plants, workers are required to wear a complete suit to minimize exposure to acrylonitrile. In addition, all employees exposed to acrylonitrile at concentrations at or above the action level of 1 ppm are required to be part of a medical surveillance program. The protective equipment worn to reduce/eliminate exposure to acrylonitrile, a more volatile material, should minimize worker exposure to thiodipropionitrile.
Protective equipment includes impervious gloves and an apron to prevent skin contact, chemical splash-proof goggles or a face shield, and a NIOSH approved respirator when there is potential for inhalation exposure (Cytec Industries Inc., 1997).